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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/535,692	09/14/2005	Annick Harel-Bellan	BDM-05-1130	9223

35811 7590 08/01/2008

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
08/01/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/535,692	HAREL-BELLAN ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,19,21-24 and 26-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,19,21-24 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5-14-08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 4-14-08.

Claims 17, 19, 21-24, and 26-29 are pending in the instant application.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Rejections Necessitated by Amendments

Applicant's arguments with respect to claims 17, 19, 21-24, 26, and 27 have been considered but are moot in view of the new ground(s) of rejection set forth below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17, 19, 21-24, and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taira et al (US 2004/0002077) in view of Srivastava (USPN 5,948,646) for the reasons of record set forth in the Office action mailed 12-13-07 and for the reasons set forth below.

The claims are drawn to compositions and methods for transcribing RNAi in cells comprising providing eukaryotic cells at least one molecule of a nucleic acid comprising sense and antisense sequences of RNAi placed under control of a single transcription promoter, which sense and antisense sequence are separated by an intervening sequence flanked by lox sites, and which intervening sequence comprises a transcription stop site and a gene encoding an antibiotic resistance marker which is optionally neomycin, wherein the intervening sequence is framed at each end by a pair of lox sites, and which method comprises providing Cre to cells and the expressed Cre produces site specific recombination and removal of the intervening sequence, thereby generating a construct encoding self complementary RNAi molecule under control of a single transcriptional promoter for subsequent gene silencing.

Taira et al teach methods and compositions comprising introducing a nucleic acid (DNA) molecule into a eukaryotic cell, which nucleic acid molecule comprises an antibiotic resistance marker, and further comprises a sense and antisense sequence optionally under control of a single transcriptional promoter, which sense and antisense sequences are separated by a stop codon, and which nucleic acid sequence is flanked

by lox sites, and which method comprises providing Cre to cells and the Cre produces site specific recombination elimination of the intervening sequence, whereby upon recombination and in the presence of Cre, or upon Cre expression, RNAi is formed in the cell (see abstract, paragraphs 0023-0044, figures 1, 3-7, 10, paragraphs 0117-0119, 0126, claims 14, 17, 18, 22, 25-27).

Taira et al teach compounds and methods of expressing RNAi in cells using an siRNA expression system, wherein said system comprises loxP sequences in the form of any one of the following (a) to (d) so that the expression can be controlled:

(a) the promoter comprises DSE and PSE with a space therebetween, and in the space two loxP sequences, one in the vicinity of DSE and the other is the vicinity of PSE;

(b) the promoter comprises DSE and PSE that are located to maintain the promoter activity, a loxP sequence therebetween, and another loxP upstream of DSE or downstream of PSE;

(c) two loxPs are located so as to interpose the antisense code DNA or sense code DNA; and

(d) two loxPs are arranged so as to interpose a linker comprising a **stop** sequence (e.g. TTTTT);

the siRNA expression system according to (16) or (17), wherein the antisense and sense code DNAs are maintained in a vector molecule;

FIG. 17 is a diagram showing an example of the construction for controlling siRNA expression using the Cre-lox system.

FIG. 28 is a diagram representing the stem-loop siRNA expression system containing two loxPs that interpose the linker portion containing the stop sequence.

Furthermore, in the case of the stem-loop siRNA expression system, it is possible to provide two loxPs in the linker portion so as to interpose the stop sequence (e.g. TTTTT). Without CRE protein, transcription from the promoter is terminated at the stop sequence in the linker portion, leading to the suppression of siRNA production. CRE protein induces the recombination between loxPs to displace the stop sequence, leading to transcription of antisense and sense code DNAs to produce the stem-loop siRNA (cf. FIG. 28). (see paragraphs 0030-0035, 0081, 0098, and 0118).

Taira et al do not teach antibiotic resistance markers that are placed in the intervening sequence between the sense and antisense sequences of the nucleic acid construct.

Srivastava (USPN 5,948,646) teach the use of antibiotic resistant genes in expression plasmids, including hygromycin and neomycin resistant genes, to enhance selection of cells containing these antibiotic resistant selection markers (e.g. to enrich for transfected from untransfected cells) (see bridging paragraph, col. 16-17).

It would have been obvious to one of ordinary skill in the art to design and synthesize nucleic acid (DNA) molecules for methods of expressing RNAi in cells comprising introducing a nucleic acid molecule comprising a sense and antisense

sequence under control of a single promoter, which sense and antisense sequences are separated by a stop codon, and which nucleic acid sequence is flanked by lox sites, whereby in the presence of, or upon Cre expression, RNAi is formed in the cell, because the method of producing RNAi molecules using a single transcription site, interposed with a stop codon between the sense and antisense sequences were taught previously using the nucleic acid constructs previously taught by Taira.

One would have been motivated to insert a neomycin resistant gene into this construct in order to determine the level of transfection of the nucleic acid construct in a target cell, and to select for cells comprising this construct. One of ordinary skill in the art would have expected that, prior to recombination, cells comprising this construct would be selected in the presence of neomycin, therefore enriching transfected cell populations, and neomycin resistant marker were well known in the art at the time the instant invention was made. One of ordinary skill in the art would have been motivated to devise such a construct comprising a sense and antisense sequences flanked by Cre sites, so that, upon recombination, an RNAi construct would be formed for target gene inhibition from the two, self complementary sequences expressed as a single molecule from transcription of the transfected nucleic acid construct. One of ordinary skill in the art would have expected that, upon homologous recombination in the presence of Cre, or upon Cre expression, the resulting RNAi molecules would assemble, and target gene inhibition occurs.

One would have been motivated to include antibiotic resistant marker gene in the nucleic acid construct as a means for selecting transfected cells from those not bearing

the RNAi-generating construct. To place the marker within the intervening sequence between the sense and antisense sequences, rather than elsewhere on the vector but under control of the transcriptional promoter, would be the result of a design choice for the nucleic acid construct because this marker would function as a selection marker in this or another part of the vector, once it was transcribed. One would have a reasonable expectation of success in using this design choice of a nucleic acid construct in selecting for transfected cells using the neomycin marker because neomycin resistant markers were well known in the art at the time the instant was made, as taught by Srivastava and other in the art. One would also reasonably expect that, upon recombination, a single, self-complementary RNAi construct will be transcribed and be formed in the transfected cell.

For these reasons, the instant invention would have been obvious to one of ordinary skill in the art at the time the instant invention was made.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz, can be reached on (571) 272-0763. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
7-17-08

/Jane Zara/

Primary Examiner, Art Unit 1635